REMARKS

Claims 1-33, 77, 83-108 and 118-126 are now pending in the application. Claims 109 and 112-117 are cancelled herein. Claims 83, 88-92, 95, 96, 98-100 and 110-111, 113-126 are currently under examination. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

Applicant would like to thank Patent Examiner Lynn Bristol for her time and courtesies extended during a telephonic interview conducted on October 15, 2007 in which the various §112 rejections as well as the Examiner's suggestion that specific examples are required to demonstrate the phrophylactic effect of the DNA Vaccibodies against different multiple myeloma cells, including human cell lines were discussed.

OBJECTIONS MAINTAINED

SPECIFICATION

The objection to Figure 8-11 for disclosing the linker sequences, $(GlyGlyGlySerSer)_3$ (Figures 8 and 9 and $(GlyGlyGlyGlySer)_3$ (Figures 10 and 11, with out reference to a SEQ ID NO is maintained.

Applicant has amended the respective figure legends as recommended by the Examiner. Applicants accordingly request that the present rejection be reconsidered and withdrawn.

REJECTIONS MAINTAINED

REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH

Claims 118, 121, 122 and 124-126 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record as set for the in the Office Action of 11/7/06 and hereafter. This rejection is respectfully traversed.

Claim 118 is drawn to a nucleic acid of claim 83, formulated for administration to a patient to induce production of said recombinant antibody-based molecule. The Applicants respectfully submit that the requirements of 35 U.S.C. 112, first paragraph, specifically, providing an enabling disclosure for the breadth of scope of Claim 118 has been adequately met. Claim 118 requires that the construct in Claim 83 be expressed when administered to a patient. The specification on page 28 as originally filed, provides adequate and enabling disclosure for one of ordinary skill in the art to administer the recombinant constructs of Claim 83 in a manner to generate the construct's expression product as shown in Example 5, pages 34 and 35 of the specification. Specific Vaccibody protein to idiotypic Fv from MOPC315.4 tumor was detected in sera of mice in significant amounts, as recited in the specification on page 34 and 35.

Claims 118-126 are directed to a pharmaceutical composition comprising a nucleic acid according to claim 83, and a vaccine composition comprising an immunologically effective amount of the nucleic acid according to claim 83.

As interpreted by the Applicants, the Examiner is basing the lack of enablement rejection on the perceived premise that the Applicants have not provided sufficient

teachings to one of ordinary skill in the art how to treat or prevent a cancer much less a myeloma "or inducing a prophylactic T- or B-cell immune response in a *human patient* with a *nucleic acid* of the claims examined in the Office Action of 11/7/06..." (Action at 6-7) Applicants have understood the present rejection alleged by the Examiner to be based on a lack of working examples that teach one of ordinary skill in the art how to prevent or provide a preventative or prophylactic response against multiple myeloma in a patient using the recombinant constructs recited in the claims. Moreover, the Action states that there are no working examples of practicing administration of the nucleic acid by injection and electroporation which results in a) induction of an immune B- and T-cell response or b) a reduction in a cancer, i.e. to induce tumor immunity to prevent tumor occurrence or recurrence using the nucleic acid as originally examined. (Action on pages 6 and 7).

At the outset, Applicants apologize for not transmitting the Stevenson et al., reference and have resubmitted this reference as requested by the Examiner. Applicants maintain that a significant number of scientific papers have discussed genetic immunization, with DNA plasmas, for example, Stevenson *et al.* 2004 (from PNAS, attached as a courtesy copy herewith) which describes more recent experiments with DNA vaccination.

Applicants have provided an enabling disclosure for all of the claims reciting a pharmaceutical composition. Applicants have provided several examples of how to use the claimed invention, i.e. the nucleic acid for use in a pharmaceutical composition. For example, methods of preparing the nucleic acid and other components for the pharmaceutical compositions are described in Methods and Materials section for

making the compositions, particularly for the myeloma specific antigens on pages 20-28. Similarly, the Applicants have adequately described how to use the pharmaceutical compositions to treat and prevent myeloma by specifically teaching one of ordinary skill in the art how to inject the pharmaceutical composition intra muscularly for example, and electroporate the construct for expression in vivo. (See for example, DNA Vaccination and electroporation, page 28, par. [0064] internal references cited therein).

Applicants have further provided enabling disclosure of genetic vaccine compositions as recited in claims 124-126. Applicants submit that Examples 5 and 6 adequately teach one of ordinary skill in the art how to make the genetic vaccine constructs for administration into muscle and expression of the genetic construct using electroporation which is an established technique. (Stevenson et al.). The specification as filed, for example, in Example 5, demonstrates that the immunization with a genetic vaccine construct induced a robust T cell and B-cell response and in particular, antibodies reactive to the antigenic unit of the Vaccibody encoded by the genetic vaccine construct. The antigenic unit in Example 5 is an idiotype derived from the murine multiple myeloma MOPC315.4 cell line. There is no limitation on the sequence of the antigenic unit to be constructed and can the antigentic unit be tailored to different tumor specific antigens known in the art. The Application specifically teaches how to make and use the genetic vaccine constructs and has adequately shown that they are effective in generating T-cell responses that are coupled with B-cell involvement in generating antibodies to tumor specific antigens. (See Specification, Example 5 and 6 pages 34 and 35).

Applicants submit that a careful analysis of the Wands Factors described in the MPEP section 2164.01(a) reveals that the Applicants have enabled the full breadth of the claimed subject matter of Claims 118, 121, 122 and 124-126.

At issue in the present rejection is whether there is sufficient teaching to one of ordinary skill in the art to use the compositions claimed to effect pharmaceutical application, and immune B- cell and T-cell generation and vaccine protection.

Applicants further submit that Claims 118, 121, 122 and 124-126 are fully enabled by the working examples, and by proffered teachings in the art, that such subject matter recited in the claims above have been shown to perform as claimed in the present application in references that are not prior art to the claimed inventions described herein.

Applicants respectfully submit that the working examples in the specification as filed are fully enabling as they are correlated with the full scope of the disclosed and claimed methods of use. (Pharmaceutical use and vaccine use, i.e. treating and preventing the myeloma cancer). Applicants base their assertion due to the fact that the animal model used by the Applicants in enabling the methods of use and compositions recited in the rejected claims is recognized as a particular model which correlates to a specific condition (multiple myeloma) and should be accepted by the Examiner as correlating to treatment and prevention in the same model unless the Examiner can proffer evidence as to why the animal model used by the Applicants does not correlate to treating and preventing multiple myeloma. Applicants have provided in support of such an acceptance of the art for the use of the Applicants disclosed animal model as a correlative and predictive model, at least 3 references showing efficacy against both

myeloma and lymphoma and for constructing similar Vaccibody molecules expressing human antigenic sequences derived from myeloma patients.

Applicants respectfully submit, that as far as a molecular model for tumor biology relating to multiple myeloma, the murine MOP315.4 cell line has been extensively studied as a multiple myeloma antibody model for over 35 years. (Eisen H N, Simms E S, Potter M. *Biochemistry.* 1968;**7**:4126–4134, Schulenburg E P, Simms E S, Lynch R G, Bradshaw R A, Eisen H N. *Proc Natl Acad Sci USA.* 1971;**68**:2623–2626. and Eisen H N, Reilly E B. *Annu Rev Immunol.* 1985;**3**:337–365.) The Ig produced by the murine model used in the present specification is well characterized and is considered by one of ordinary skill in the art to be highly relevant in studying myeloma cells lacking MHC class II molecules. Applicants respectfully submit, that the mouse cell line MOP315.4 is one in which correlative prediction in other models can be made and further, due to the restricted nature of possible cell lines for studying tumor cells lacking MHC class II molecules, the Applicants results and methods of practicing the invention described in the Methods and Materials sections and particularly in Examples 4-6 are highly correlative of results performed with other cell lines, whether they are xenogeneic or human clinical isolates of other multiple myeloma tumor cells.

Applicants submit that the Claim 122 and 124-126 are fully enabled by the specification as originally filed. Claim 124 is drawn to a vaccine composition comprising an immunologically effective amount of the nucleic acid according to claim 83. As described above, Applicants respectfully submit that the term vaccine connotes prevention and/or a diminishment of a disease in comparison to no vaccine at all. The present specification provides suitable and ample evidence of an enabling disclosure of

how to make and use a vaccine formulation to generate a prophylactic response in a mouse model that is correlative to similar efficacy in other models. The specification describes how to immunize Balb/c mice with the Vaccibodies in DNA form. The electroporation of the DNA construct generated anti-idiotypic antibodies 14 days after administration. See for example, Figures 21a and Fig. 21b. Figs. 22 and 23 demonstrate a strong protective effect (Prophylactic effect) when the same mice were challenged with tumor cells (MOPC315.5 myeloma cells) as compared to saline controls. The vaccine effect was to reduce and then eliminate the tumor mass after approximately 20-28 days after challenge. Applicants submit that this Example in the specification provides adequate enabling disclosure that the administered DNA constructs provide a prophylactic effect in protecting the mice from developing tumors after challenging with a tumor cell line. (See Example 5 and 6, pages 34 and 35).

Applicants have provided further evidence of prophylactic and preventative effects using the pharmaceutical and vaccine compositions of Claims 122, 124-126 in Brunsvik, A., et al., *Chemokine –idiotype fusion DNA vaccines are potentiated by bivalency and xenogeneic sequences*, Blood, published online, May 31, 2007; Schjetne, K.W., et al. *Delivery of antigen to CD40 induces protective immune responses against tumors*, J. Immunol. 2007, 178:4169-4176; and Fredriksen, A. B., et al., *DNA vaccines increase immunogenicity of idiotypic tumor antigen by targeting novel fusion proteins to antigen-presenting cells*, Mol. Therapy., Accepted October 26, 2005. All three articles are provided for the Examiner herein. Further evidence of the ability of the Vaccibodies to confer prophylactic responses can be found in the manner and degree of T-cell activation and that the targeting unit encoded by the Vaccibodies can be recognized by

antigen presenting cells. (See Specification, Example 2, par. 0072 & 0073, page 32 and Schjetne , K. W. et al., page 4172, col. 2). These mechanisms of immune activation are consonant with the classical immune activation of a foreign peptide or protein vaccine, and are shown to provide examples of T-cell and B-cell immune responses that lead to protective or prophylactic protection against specific tumor cells.

With respect to the Examiners contention that Claims 118, 121, 122 and 124-126 are "not any more enabled for an intended use in gene immunization or gene therapy, because the instant specification does not teach how one skilled in the art could achieve with any degree of predictability the equimolar expression of each monomer unit from a different vector much less that the two monomer units could specifically dimerized in vivo to form a dimeric antibody." The Applicants respectfully traverse this rejection.

Applicants respectfully submit that claims 118, 121, 122 and 124-126 do not require two different monomer units in order to obtain the desired expression of a dimeric antibody. The dimmers in the present application are formed from homodimers, which assemble spontaneously from the expression products of one single vector (due to the presence of the dimerization unit in the monomers) In Example 5 and 6, the cell lines used as a host are transfected with one single vaccine vector construct which provided expression of functional homodimers. It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work. For example, Figure 19 of the application shows that one vector would produce the antigenic unit and the targeting unit. These expressed units would dimerize through the dimerization unit also produced with each copy of the units. Hence, the Applicants respectfully submit that the rejection of Claims 118, 121, 122 and 124-126 under 35 U.S.C. § 112 1st

Paragraph does not require the Applicant to teach how "one skilled in the art could achieve with any degree of predictability the equimolar expression of each monomer unit from a different vector much less that the two monomer units could specifically dimerize in vivo to form a dimeric antibody" (Action, page 8).

REJECTION UNDER 35 U.S.C. § 102

The rejection of Claims 83, 88-92, 96, 98, 109-117, 119, 120 and 123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US20050069549); published March 31, 2005; filed Jan. 14, 2003) is maintained for reasons of record as set forth in the office action of 11/7/06 and hereafter. This rejection is respectfully traversed.

Applicants respectfully assert, that the claimed nucleic acid construct in Claim 83 is one where the antigenic unit is separated by a hinge region and a dimerization motif. Is not disclosed in Hermann. Although Hermann may discuss the use of CH3 domains (See for example par. [0116], on pages 14 -15.) Hermann fails to disclose the spatial arrangement of the claimed nucleic acid construct of Claim 83.

NEW GROUNDS FOR OBJECTION

CLAIM OBJECTIONS

Claims 109 and 112 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicants respectfully assert, that the cancellation of Claims 109, 112 and claims depending therefrom have corrected the Claim deficiencies and obviate the present objection.

Accordingly, Applicants respectfully request that the objections be reconsidered and withdrawn.

NEW GROUNDS FOR REJECTION

REJECTION UNDER 35 U.S.C. § 112, 2ND PARAGRAPH

Claims 83, 88-92, 95, 96, 98-100 and 109-126 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

Applicants respectfully assert that the claim amendments herein have overcome the 35 U.S.C. § 112, second paragraph, indefiniteness rejections for lack of antecedent basis, particularly described in items 20(a), 20(c), and 20(d).

Applicants submit that "a hinge region" is not indefinite as recited in Claim 83 and claims dependent thereon. The term "hinge region is adequately described in the specification for example on page 20-21. The term can encompass the h4 exon connected to the CH3 domain or can include other hinge regions commonly known for a specific Ig molecule such as h1-h4 in human Ig. Other hinge regions can include mouse hinge regions of a particular murine Ig subclass. Accordingly, the Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Applicants have cancelled Claim 109, thus rendering the indefiniteness rejection of Claim 109 moot.

Similarly, Claims 113-117 which depend from Claim 109 are hereby cancelled, rendering this rejection moot. Accordingly, the Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Claim 111, is also cancelled herein, thus rendering the present rejection of Claim 111 under 35 U.S.C. § 112, second paragraph moot.

Applicants hereby submit that the present amendments and cancellation of Claims 109-117 render the present rejection under 35 U.S.C. § 112, second paragraph overcome or moot. Applicants respectfully request that the present rejection be reconsidered and withdrawn accordingly.

REJECTION UNDER 35 U.S.C. § 112, 1ST PARAGRAPH

Claims 118, 121, 122 and 124-126 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention. This rejection is respectfully traversed.

The Examiner has alleged that Claims 118, 121, 122 and 124-126 fail to comply with the enablement requirement, specifically that the specification fails to teach or disclose a cistronic vector "encoding both monomeric units that are expressed in equimolar amounts and that would allow the expressed monomeric subunits to dimerize into a dimeric antibody in vivo. This rejection is respectfully traversed.

Applicants have discussed supra, that the exemplified embodiments do not require, two different monomer units to dimerize to form the dimeric antibody. The dimmers in the present application are formed from homodimers, which assemble spontaneously from the expression products of one single vector (due to the presence of the dimerization unit in the monomers) In Example 5 and 6, the cell lines used as a host are transfected with one single vaccine vector construct which provided expression of functional homodimers. It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work. For example, Figure 19 of the application shows that one vector would produce the antigenic unit and the targeting unit. These expressed units would dimerize through the dimerization unit also produced with each copy of the units. Hence, the Applicants respectfully submit that the rejection of Claims 118, 121, 122 and 124-126 under 35 U.S.C. § 112 1st Paragraph is inappropriate with respect to teaching required equimolar amounts of different monomeric units. Only one type of antigenic unit and one type of targeting unit is sufficient to generate potent T- cell and B-cell responses and prevent the formation of a multiple myeloma tumor and death of an animal due to multiple myeloma as shown in Example 6.

With respect to the Examiners allegation that the specification does not enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation, Applicants response has been discussed above with respect to the maintained rejection of Claims 118, 121, 122 and 124-126 above.

To reiterate Applicants' arguments to the above rejection, the specification as filed provides suitable examples for making and using the claimed inventions, including

pharmaceutical compositions comprising the genetic constructs for administration into an animal, including humans without undue experimentation. Moreover, the Methods and Materials section of the specification teach one of ordinary skill in the art how to assemble the genetic construct components. These constructs are not limited to murine gene sequences, but can also include human gene sequences that are similarly constructed together as shown for the mouse genes. The genetic construct can then be formulated into a pharmaceutical composition and injected into the muscle tissue of the patient or subject as described in the Examples section of the Applicants specification and is also discernible from the art. The specification also teaches how to electroporate the genetic vaccine construct for expression, and the Applicants provide herein Stevenson et al., which describes techniques for i.m. injection and electroporation as part of a DNA vaccination administration scheme which was known at the time of filing the present application.

The specification provides Examples 4-6 which teach one of ordinary skill in the art how to generate a robust T-cell and B-cell response by administering DNA vaccine constructs comprising the monomer units of the exemplified embodiments. Examples 5 and 6 on pages 34 and 35 demonstrate the production of a strong immune response against the antigenic target of the multiple myeloma. The natural progression of such a robust immune response in Example 5 is followed up by a showing that indeed, the genetic constructs of the presently claimed invention can be used to prevent tumor formation in an animal not previously primed for a response against multiple myeloma cancer cells MOP315.4 myeloma cells. This experiment and results verify that the disclosed methods and claimed subject matter are representative of the uses claimed in

claims 118, 121, 122, 124-126. One of ordinary skill in the art can design different antigenic units as taught in the specification to produce Vaccibodies capable of inducing an immune response and prophylactic response to other tumor specific antigens. One of ordinary skill in the art can acquire information as to suitable tumor antigens for targeting and deliver via DNA vaccination techniques, a genetic vaccine that is capable of presenting the targeted tumor antigen for T-cell and B-cell immune involvement and subsequent production of immunoglobulin in vivo to target and destroy the tumor cells.

Applicants have provided 3 journal references that further demonstrate that the genetic vaccibodies comprising DNA administration of a genetic construct disclosed in the specification as filed are effective in targeting and destroying tumor cells by activating the T-cell and B-cell immune response against the tumor antigen targeted.

The Applicants respectfully submit that the specification as filed contains adequate description of how to make and use the present inventions to the full scope of the claimed subject matter, including the pharmaceutical and vaccine protective effects of claims 122, and 124-126.

Accordingly, the Applicants respectfully request that the preset rejection under 35 U.S.C. § 112, first paragraph be reconsidered in view of the present arguments and cited references, and withdraw the present rejection of Claims 118, 121, 122 and 124-126 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

It is believed that a full and complete response has been made to all of the issues raised in the outstanding Office Action. Thus, prompt and favorable

consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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